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Using Recall Data to Assess the 510(k) Process

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- Chris Walker

Disclosures

University of Minnesota Law School	• Distinguished Professor and Practitioner • Supported in part by NSF and NIH Grants
510(k) research supported by Kauffman Foundation	• Complete academic freedom
Part time Counsel – Baker & Daniels	• Advise clients on FDA regulatory matters including 510(k) submissions and reform, PMA issues and regulatory policy issues
CEO – MR3 Medical LLC	• Start up medical device company • Probably PMA pathway if product successful

Agenda

I. Research questions
II. Research Methodology
    A. Why examine recalls
        1) Issues with other data sources
    B. Description of Research
    C. Strengths and limitations
III. Data results
    A. 510(k) and PMA products
    B. Analysis of sub populations
IV. Conclusions and open questions

510(k) Research Challenge Avoiding "Ready, Fire, Aim"

- 510(k) system subject to substantial criticism
- However, no systemic data exists assessing whether the system is working
  - Many anecdotes exist on all sides
- Changes should address real issues, not opinions
- Research needed to assess FDA's performance in clearing 510(k) devices
- Is FDA clearing unsafe products?

Specific Research Questions

Does the 510(k) review system permit products onto the market without a "reasonable assurance of safety and effectiveness"?

- Key question
- Does FDA make the "right" safety decision in product clearances?

Are there areas or concentrations of issues?

Do specific parts of the 510(k) process lead to greater or lesser risk?

Unaddressed Research Issues

Impact of 510(k) system on innovation

- Development of new ideas
- Ability to fund new ideas
- Testing and review challenges
- Review issues

Administrative and process issues

- Timeliness
- Review processes
- Certainty and transparency

Impact of slow or uncertain reviews on patients

Methodology

Methodology

Review all Class I recalls for 5 year period

- Calendar years 2005-2009
- Class I recalls represent highest safety risk
- FDA, not industry, determines classification
- Substantial data available

Recalls identify new issues or problems

- All devices have risks that should be balanced with product benefit at approval/clearance
- Using recalls eliminates known and accepted risks from the assessment

Key Methodology Observations

- While not perfect, Class I recalls provide best safety related performance measure of the 510(k) system
  - Mandatory reporting
  - FDA oversight
  - Permits one to separate review issues from non-review issues
- MDR data not a good tool
  - Reports include known risks
  - Highly variable reporting rates
  - Inaccurate and unconnected events reported
  - No quality control or confirmation
  - MDRs are anecdotal reports
- Number of products involved in recall not useful
  - No denominator
  - Can't separate single and multiple use products
  - Can't determine actual failure rate or rate of actual harm
  - Includes non-defective products

Why Use Class I Recalls?

- Class I recalls represent FDA's view of serious safety issues
  - **"Class I recall:** a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death."
  - Includes risks of death
  - Includes issues with less than 1% risk of failure
- Class II represents temporary or reversible medical issues or remote risks
- Class III – no safety issues
- FDA assigns recall class

Methodology
Key Data Sources

FDA data bases

- Recall database
- 510(k) and PMA databases
- Product classification
- New TPLC database

2009 GAO Report and related materials

Ancillary internet searches

Several calls to companies and FDA

Methodology and Data

474 total recalls identified

- Used date listed on FDA recall

Multiple records for one event

- Different sizes, model numbers or trade names

Consolidated multiple records into one

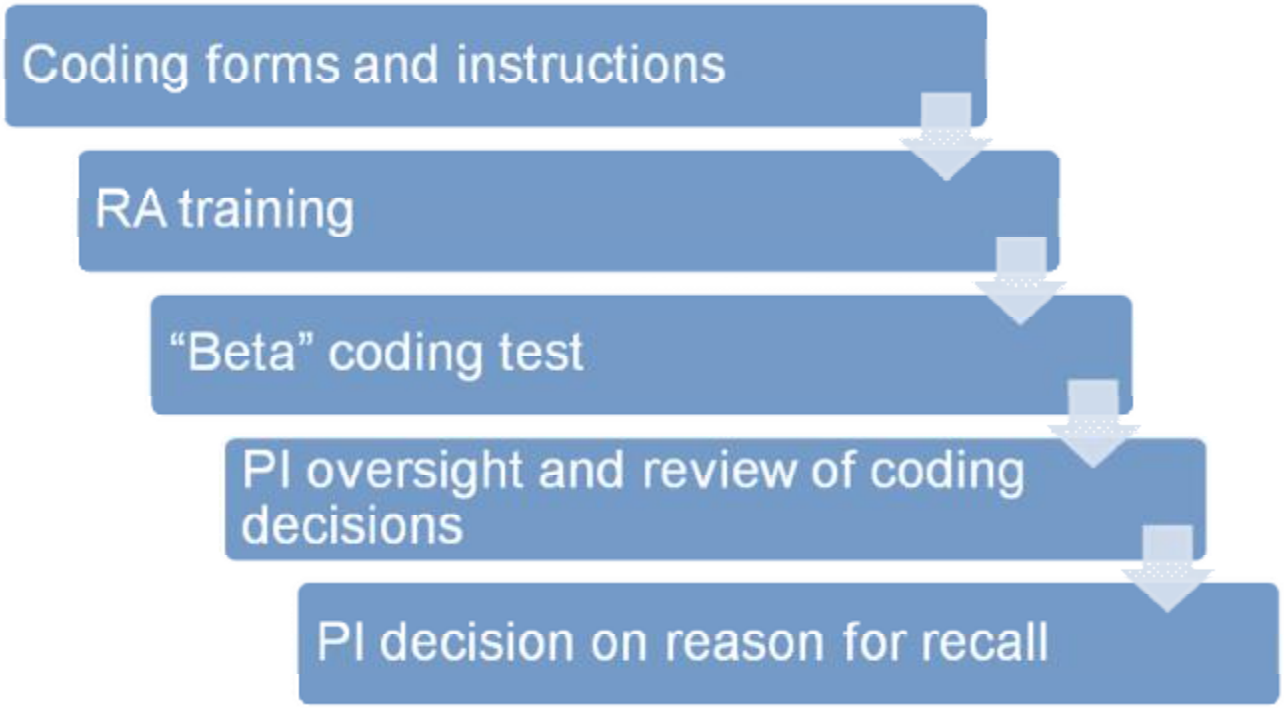
118 unique Class I recalls

Coded all recalls

- Data tied to FDA records
- Data audited and confirmed

Methodology and Data

Data collection system established



Data entered and checked

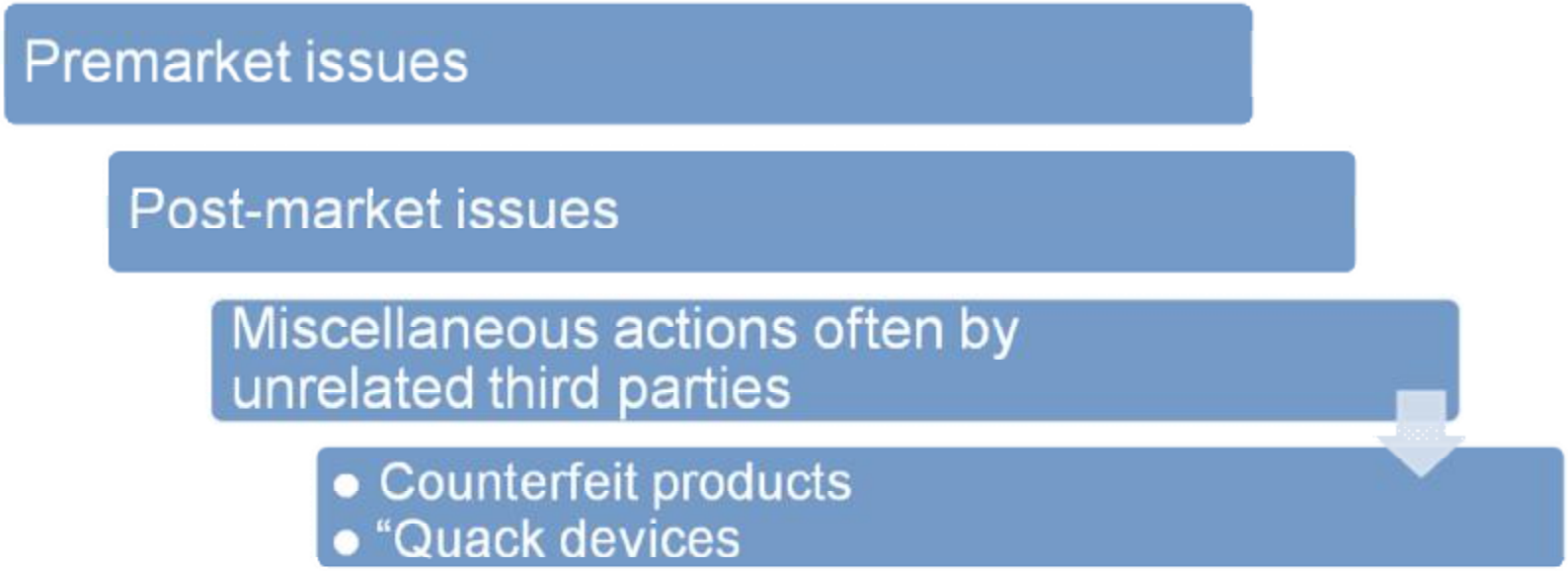
Methodology

Data coded included:

- Product name
- Recall date
- Approval/clearance pathway
  - PMA
    - Type of sPMA
  - 510(k)
    - Traditional
    - Abbreviated
    - Special
- Implantable
- Reason for recall
- Product class (I, II or III)
- CFR section and subsection
- Third party review
- 3 letter product code
- Medical specialty
- Dates
- Reported deaths

Methodology

Recalls are caused by one of three broad root causes

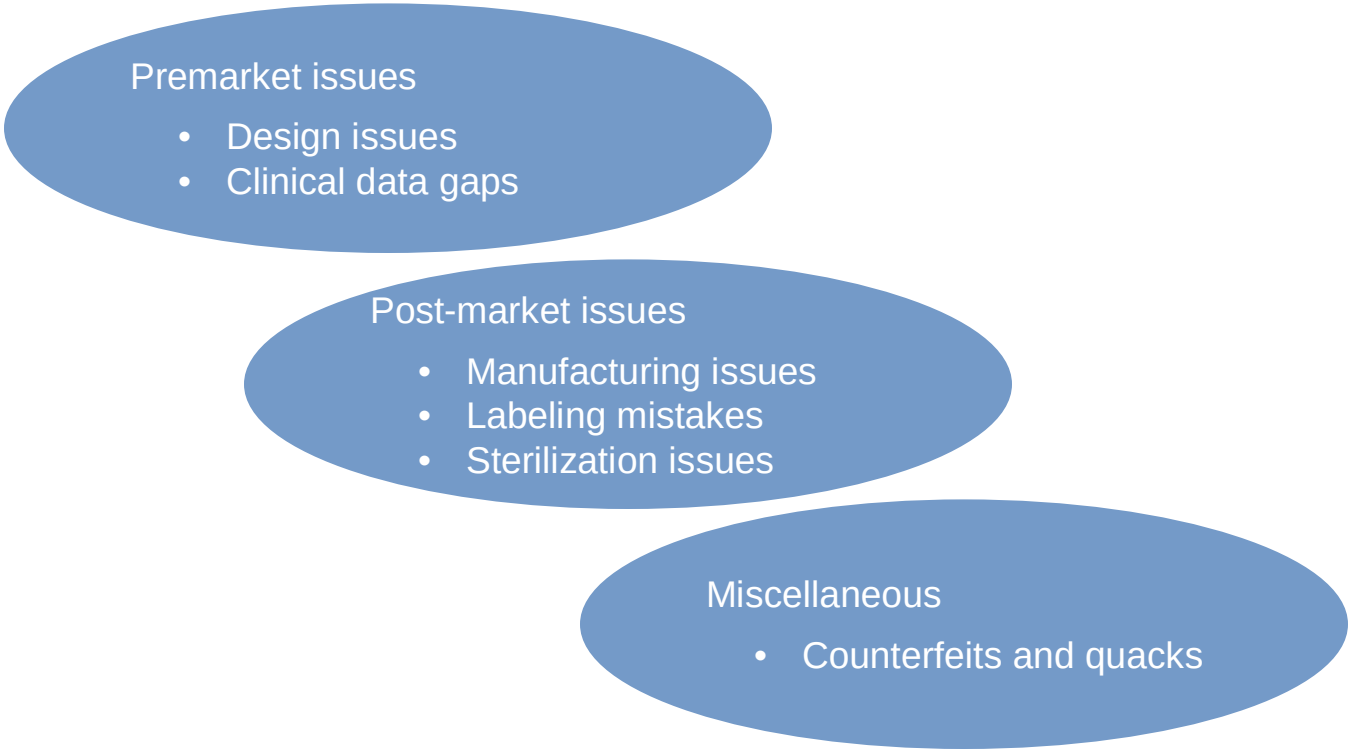


Robustness of FDA review process relates only to the first set of issues

Need to determine root cause as initial analysis step

Methodology

13 categories for reason for recall



PI reviewed and assigned all reasons for recalls

Blind review of 10% of recalls

Challenges to Methodology

- Data from FDA data bases used – assumed accuracy of FDA data
  - Sampling supported FDA data
- There may be “missing” recalls
  - Violation of law
  - Probably aren’t major events
- Emphasis on Class I recalls
- Use of FDA’s recall classification as the risk assessment
  - Consistency of FDA determinations

Data Analysis

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Data Overview

118 unique Class I recalls

- 6 counterfeit/quack recalls

112 core recalls

- Most recalls were initiated in the 2005-2009 period
- 4 were initiated earlier but not entered by FDA until 2005-09
- Average of 22.4 Class I recalls per year
  - 50,000 + listed devices (2009 GAO Report)
  - 0.2% recall rate over 5 years

Adequate data available on vast majority of all recalls

Data from FDA databases used – assumed accuracy of FDA data

- Sampling supported FDA data

Date Recall Conducted

Year	Number of Recalls
2001	1
2003	1
2004	2
2005	27
2006	16
2007	23
2008	13
2009	35

Occasional delays in posting recall

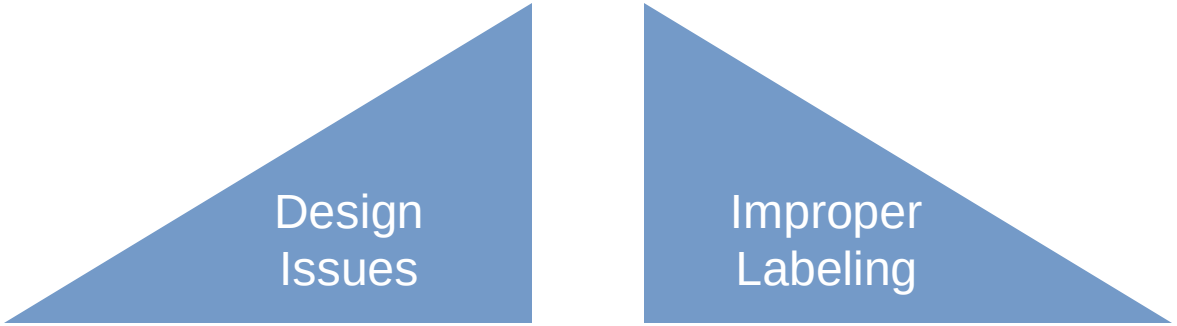
Vast majority of recalls (96.6%) occurred within 5 year data period

A few 2008 or 2009 recalls may not have been posted

Any such timing differences should be irrelevant to analysis

Causes of Recall Critical

510(k) system can only be expected to prevent "premarket" issues



Post-market issues such as manufacturing errors are a separate issue

Any assessment of the correctness of 510(k) clearance decisions or robustness of 510(k) system should look at premarket issues only

Primary Reason for Recall

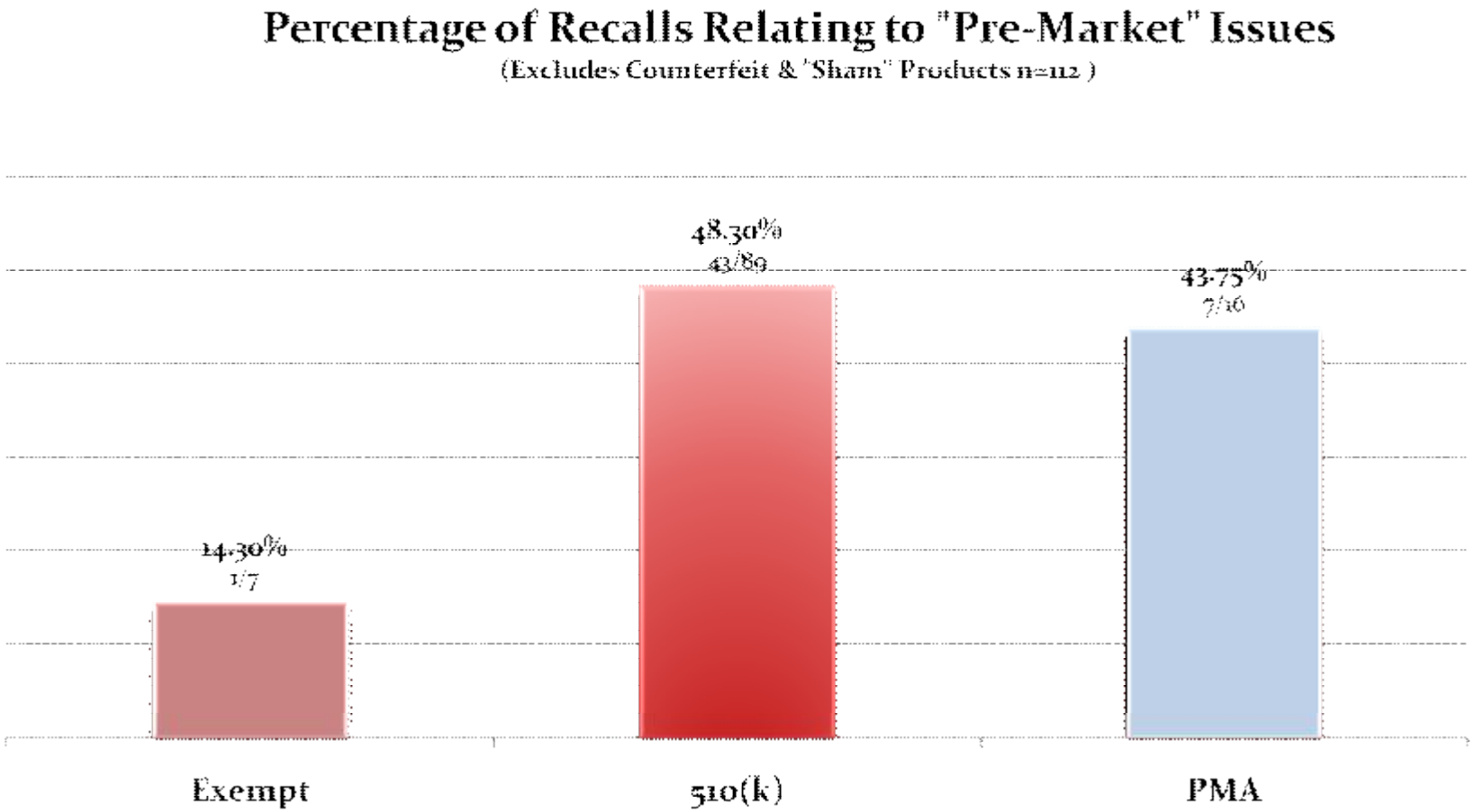
(N = 118)

Primary Reason for Recall	PMA	510K	Class 1	Other or Unknown	TOTAL
Manufacturing	6	31	2	1	40
Labeling Error	0	4	0	0	4
Design Issue	6	25	1	0	32
Software Design	1	9	0	0	10
Software Manuf. Failure	0	2	0	0	2
Supplier Issue	2	5	0	0	7
Failure to Identify Clinical Risk	0	0	0	0	0
Failure to Warn/Inadequate Instructions	0	8	0	0	8
Missing Parts	0	0	0	0	0
Sterilization	1	4	2	0	7
Regulatory Violation	0	1	1	0	2
Packaging/Handling	0	0	0	0	0
Other (Counterfeit, Sham)	0	6	0	0	6

Recalls by Approval Pathway and Recall Reason (n=118)

	Total Recalls	Recalls for Pre-Market Issues	Recalled for Post-Market Issues	Recalled for Other Issues	Percent of Recalls to Total Recalls
Class I or u/k	7	1 (14.2%)	6 (85.7%)	0 (0%)	5.9%
510(k)	95	43 (45.3%)	46 (48.4%)	6 (6.3%)	80.5%
PMA	16	7 (43.8%)	9 (56.3%)	0 (0%)	13.56%
TOTAL	118	51	61	6	118

Essentially 45% of Recalls Relate to Premarket Issues



Key Observations

- 55% of recalls relate to post market issues
  - Premarket review systems irrelevant to these issues
- Design issues (including software design) are the major cause of premarket issues
  - ~75-80% of 510(k) premarket recalls are design issues
- Role of QSR (design controls, etc.) is critical
- Role of bench testing and design controls to identify design issues without endangering patients is important
  - Let's avoid human experimentation whenever possible
- Improving QSR related design control and validation could have a substantial positive effect

Observations

- No recalls identified relating to newly discovered clinical risks
  - Inadequate labeling may be a surrogate description of newly discovered risks but also includes human factor issues
    - Note no PMA labeling recalls identified
  - Approximately 7% of recalls for any such reason
- Major difference compared to pharmaceutical recalls
- Human clinical trials often used to identify clinical risks
- **Would additional human clinical studies have a significant impact on Class I safety recalls?**
  - **This data indicates very little impact**

Observations

- Supplier issues appear to be a smaller issue that I would have guessed
  - Are supplier issues “buried” in manufacturing issues?
  - Software issues are real but concentrated in a smaller subset of products
- No Class I recalls for handling, packaging, content issues
- Relatively few label mix-up issues rise to Class I significance
- Should human clinical trials be the preferred system for identifying design issues?
  - Bench testing and design controls seem better approach

Recall Rates

The absolute number of recalls is just one measure of how effective FDA is in its premarket assessments

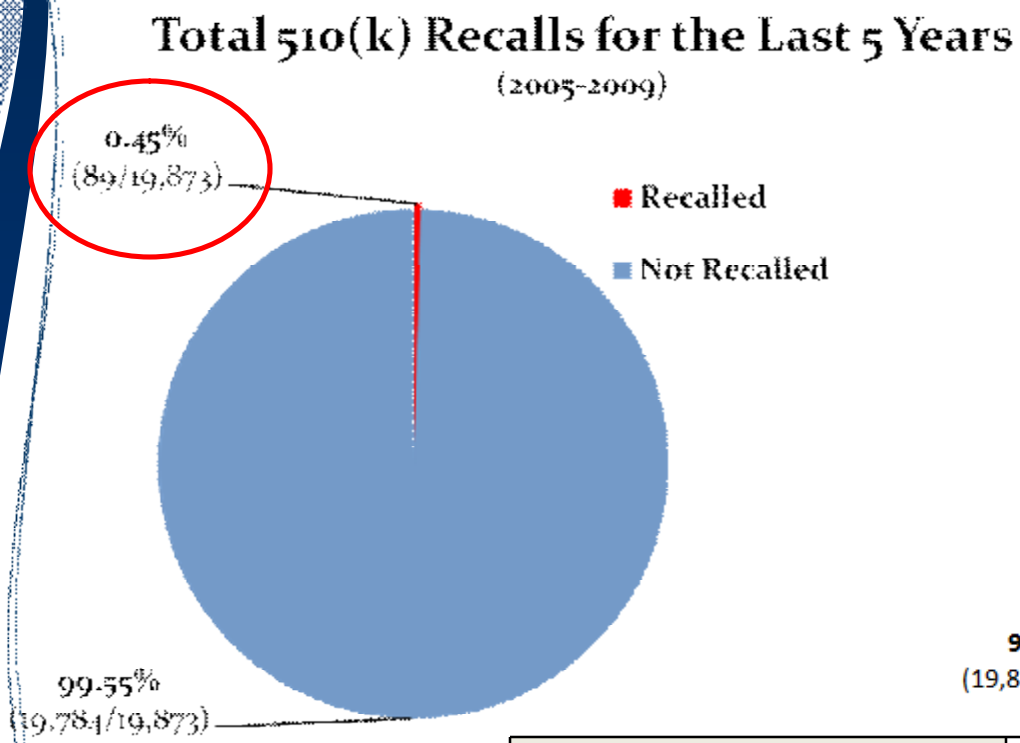
To broadly assess the robustness of FDA's review, one must look at the rate of recalls compared to submissions

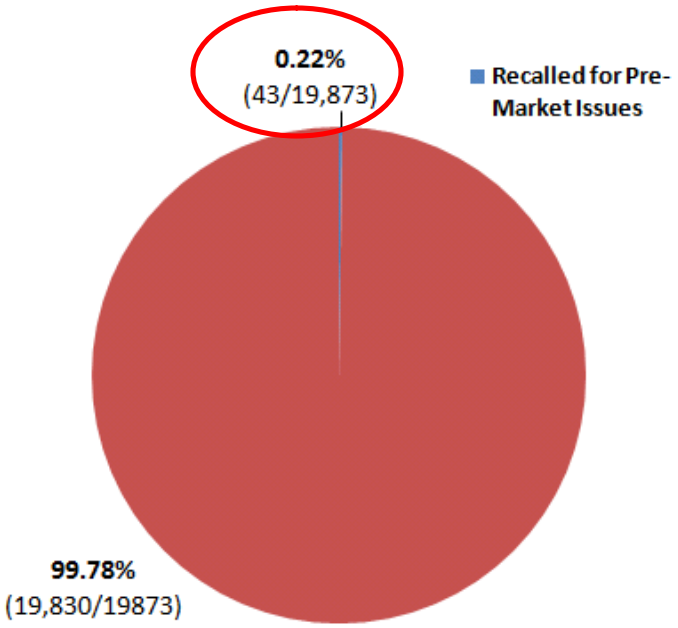
Submissions, not approvals/clearances, is the best measure of the robustness of FDA's processes as it includes situations in which the product was not cleared for market – thus eliminating any safety risk

Caveats

- Finding an exact denominator is impossible as there is no precise time relationship between submission, clearance and initiation of a recall
- These calculations use average submission rates – they are close but not exact
  - Looked at data over 10 years, created a one year average and multiplied by 5
- Submission data is the best comparator
- Using related data approaches (5 year average, 2005-2009 actual, etc.) yields similar results

Very Few 510(k) Clearances Have Been Subject to a Class I Recall





Total 510(k) Approvals in 10 years	39,747
Average Submissions in 5 year time period	19,873
Total 510(k) Recalls for 2005-2009	89
Total 510(k) Recalls for Pre-Market Issues for 2005-2009	43

Observations

- 99.78% of 510(k) submissions do not result in a Class I (safety) recall due to premarket issues
- Majority of 510(k) Class I recalls are due to post market issues
  - 55% overall
  - Role of QSR important
- Design issues are the predominate reason for premarket recalls
- Given the need to balance safety and access and the inability to be all knowing, can one expect more?

Some Interesting Comparisons

2.3% of Medicare hospitalizations result in a patient safety event

- Approximately 99,000 deaths per year
- http://www.healthgrades.com/media/dms/pdf/patientsafetyinamericanhospitalsstudy2009.pdf

2-4% risk of hospital acquired infection

- http://www.ahrq.gov/qual/nhdr09/Chap2c.htm#safety
- http://www.cdc.gov/mmwr/preview/mmwrhtml/00001772.htm
- http://www.cdc.gov/ncidod/dhqp/pdf/Scott_CostPaper

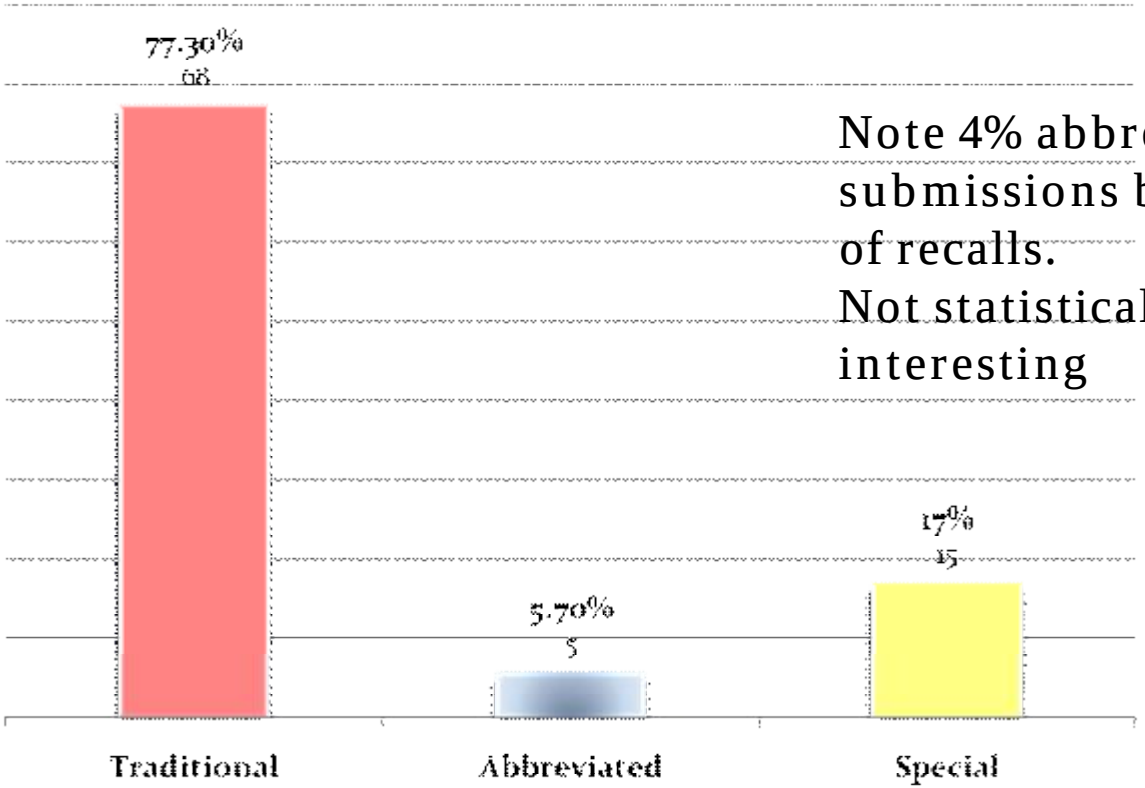
15+% of patients over 65 receive a potentially unsafe prescription

- http://www.ahrq.gov/qual/nhdr09/Chap2c.htm#safety

0.22%/0.45% recall rate for 510(k) clearances (many of which do not negatively affect a patient)

510(k) Recalls by 510(k) Approval Pathway

(excludes counterfeit products, n=88, 1 with missing information)

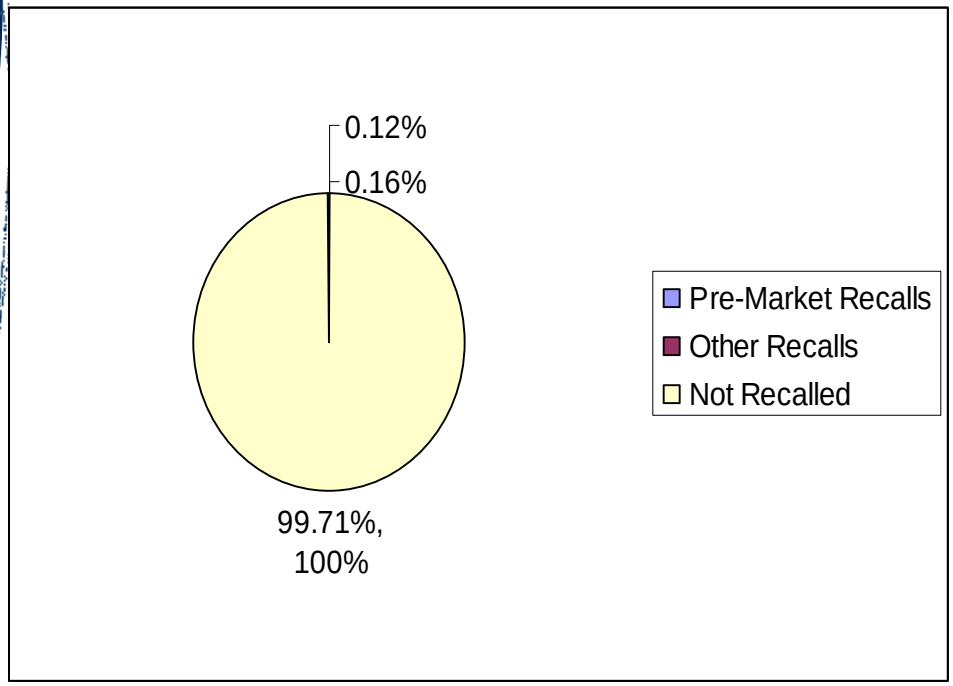


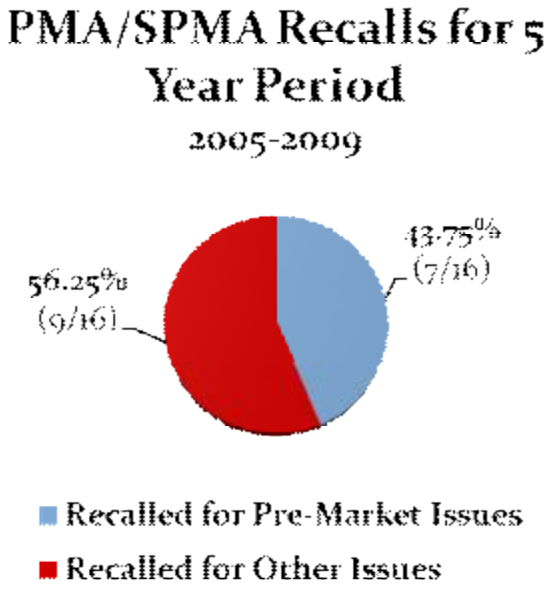
Note 4% abbreviated submissions but 5.7% of recalls.
Not statistical but interesting

Approximate Submission Percentages

77% 4% 18%

PMA/sPMA Approvals have a Similar Pattern





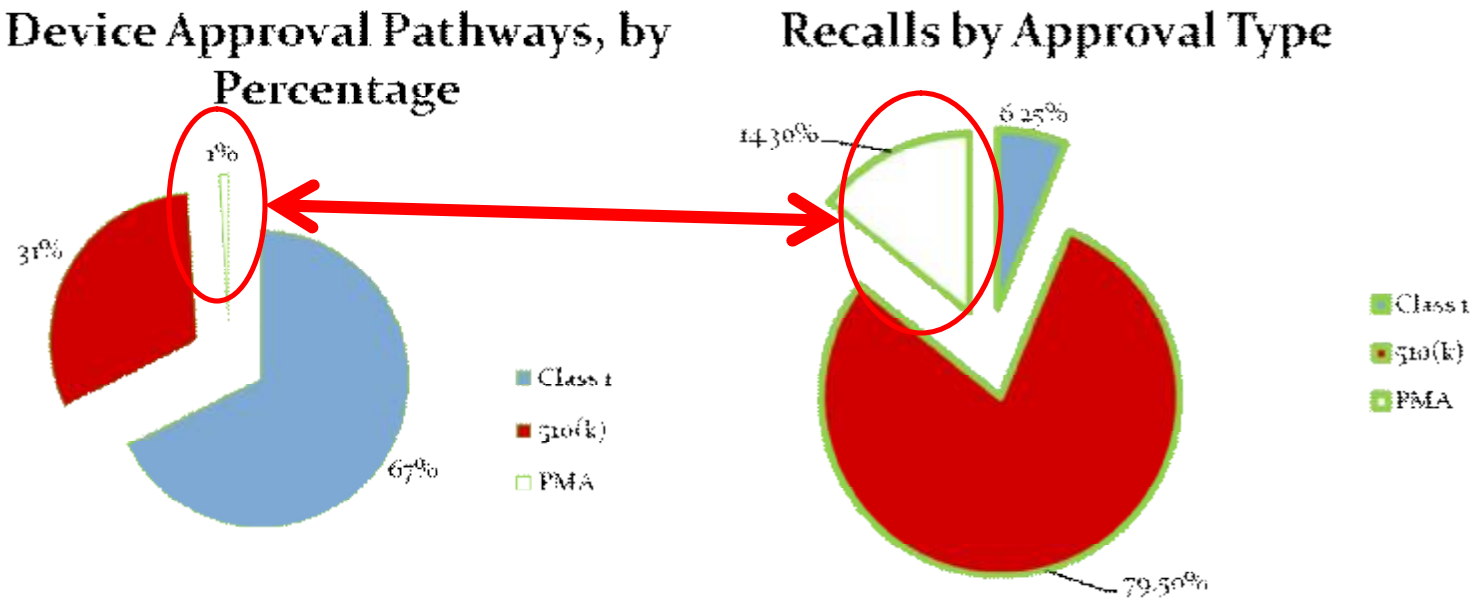
Pre-Market Recalls	**0.12%**	**7**
Other Recalls	**0.16%**	**9**
Not Recalled	**99.71%**	**5,594**
TOTAL		**5,610**

Observations

- PMA data very similar to 510(k) data
- Larger relative denominator as more changes subject to sPMA filing than 510(k) filing
  - "Could effect" vs. "could substantially effect" standard
- Does additional review under the PMA system provide same level of protection for these higher risk products?
- Do all parts of the PMA submission add to safety assessment?

Logically, PMA products account for a disproportionate number of Class I recalls

Similarly, exempt products are rarely the subject of recalls



Subtypes of sPMAs

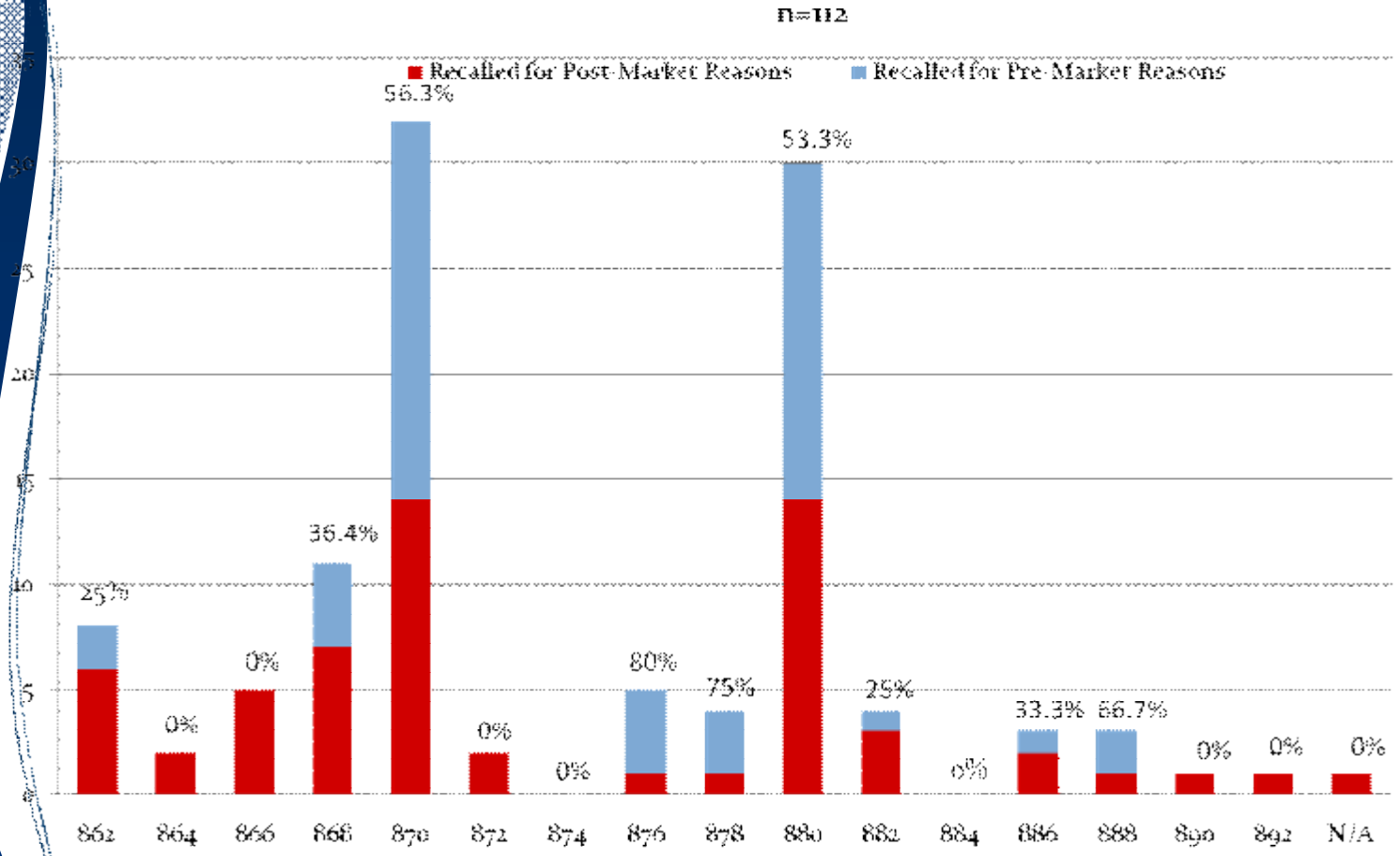
PMA Recalls for Changes Being Effected (CBE)	
Recalled for Pre-Market Issues	3
Recalled for Post-Market Issues	0

PMA Recalls for Manufactiuring Changes	
Recalled for Pre-Market Issues	2
Recalled for Post-Market Issues	0

Do Particular Device Types Pose Greater Risk?

CFR Section	Total	Recalled for Pre-Market Issues	Recalled for Post-Market Issues	% of Pre-Market Recall Issues to Total
862	8	2	6	25.00%
864	2	0	2	0.00%
866	5	0	5	0.00%
868	11	4	7	36.36%
870	32	18	14	56.25%
872	2	0	2	0.00%
874	0	0	0	0.00%
876	5	4	1	80.00%
878	4	3	1	75.00%
880	30	16	14	53.33%
882	4	1	3	25.00%
884	0	0	0	0.00%
886	3	1	2	33.33%
888	3	2	1	66.67%
890	1	0	1	0.00%
892	1	0	1	0.00%
N/A	1	0	1	0.00%

Pre-Market and Post-Market Recalls Compared, by CFR Section



Observations

- Bolus of recalls in cardiovascular (21 CFR 870) and general hospital and personal use (21 CFR 880 – a more "catch-all" category)
  - Higher rate of premarket issues than average
  - More complex devices
- Lesser concentrations in clinical chemistry and anesthesiology
- Scattering of recalls across other categories
  - No other significant patterns

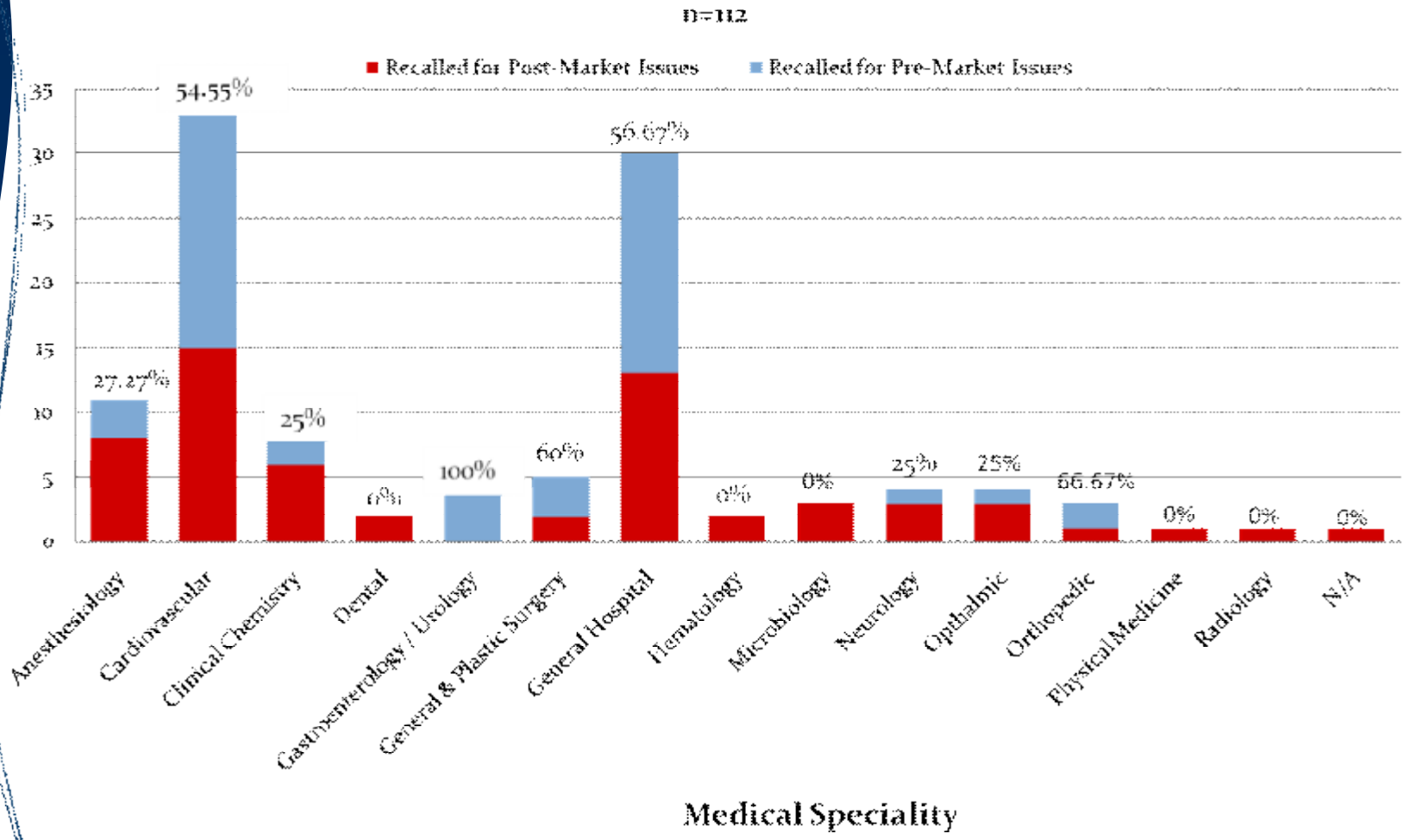
Observations

- Remarkable few Class I orthopedic recalls
  - Implantable, chronic devices
- No ob/gyn recalls
  - High risk, high profile devices
- Remarkably few Class I recalls for radiology devices
  - High profile products
- Does this data support the need for a fourth device classification?

Analyzing Recalls by Medical Specialty Demonstrates Same Pattern

Medical Specialty	Total	Recalled for Pre-Market Issues	Recalled for Post-Market Issues	% Recalled for Pre-Market Issues to Total
Anesthesiology	11	3	8	27.27%
Cardiovascular	33	18	15	54.55%
Clinical Chemistry	8	2	6	25.00%
Dental	2	0	2	0.00%
Gastroenterology / Urology	4	4	0	100.00%
General & Plastic Surgery	5	3	2	60.00%
General Hospital	30	17	13	56.67%
Hematology	2	0	2	0.00%
Microbiology	3	0	3	0.00%
Neurology	4	1	3	25.00%
Opthalmic	4	1	3	25.00%
Orthopedic	3	2	1	66.67%
Physical Medicine	1	0	1	0.00%
Radiology	1	0	1	0.00%
N/A	1	0	1	0.00%

Recalls by Medical Speciality, Percentage of Recalls for Pre-Market Issues



Looking by specific device type shows concentrations

Device Category	Number of Recalls Within the Device Category	Number of Recalls for Pre-Market Issues	Percentage of Recalls for Pre-Market Issues	Percentage of Category Recalls to Total Recalls
AED	12	6	50.0%	10.2%
Anesthesiology	11	3	27.3%	9.3%
Blood Glucose System	3	2	66.7%	2.5%
Cardiovascular	9	5	55.6%	7.6%
Catheter	11	5	45.5%	9.3%
Clinical Chemistry	5	0	0.0%	4.2%
Dental	2	0	0.0%	1.7%
Gastroenterology/Urology	4	4	100.0%	3.4%
General and Plastic Surgery	5	3	60.0%	4.2%
General Hospital	7	6	85.7%	5.9%
Glucose Test Strips	5	0	0.0%	4.2%
Hematology	2	0	0.0%	1.7%
Infusion Pump	21	11	52.4%	17.8%
Microbiology	3	0	0.0%	2.5%
Neurology	3	0	0.0%	2.5%
Ophthalmic	4	1	25.0%	3.4%
Orthopedic	3	2	66.7%	2.5%
Pacemaker	5	3	60.0%	4.2%
Physical Medicine Devices	1	0	0.0%	0.8%
Radiology	1	0	0.0%	0.8%
Sham Device	1	0	0.0%	0.8%

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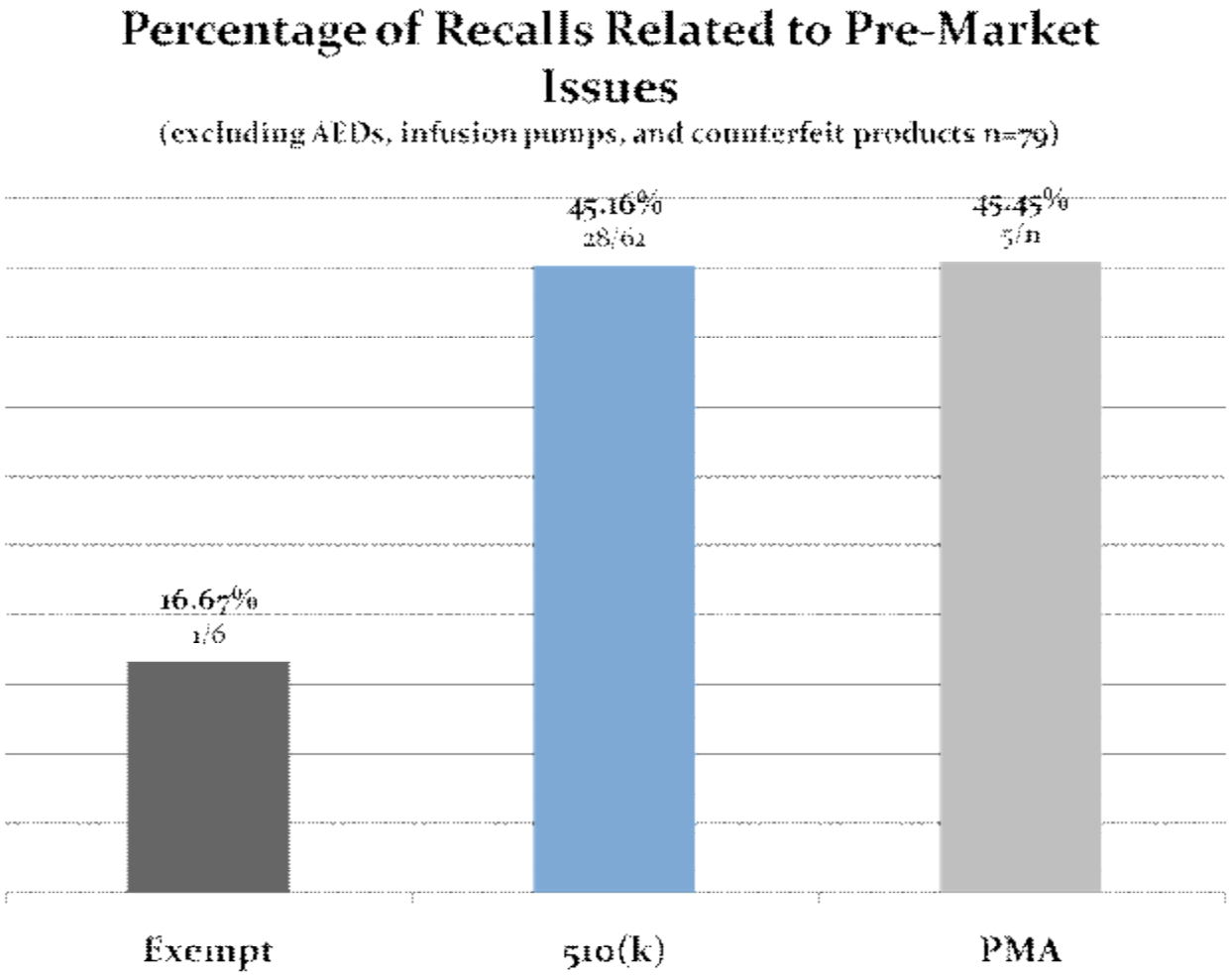
Observations

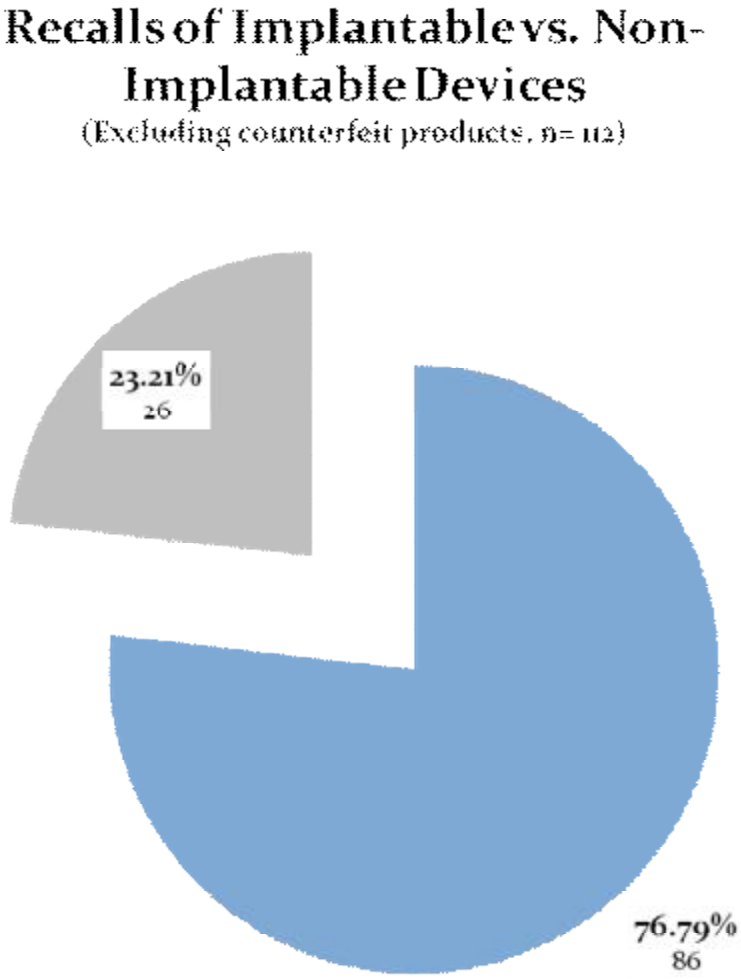
- Two product types – AEDs and infusion pumps – account for 28% of all recalls
- Five product types account for 54.2% of all recalls
- **Are product type specific guidances, special controls, etc. the appropriate response?**
  - FDA's current infusion pump initiative is consistent with this data
  - Note, however, the somewhat higher rate of recalls for abbreviated 510(k)s
- Detailed root cause investigation of these product types may be warranted



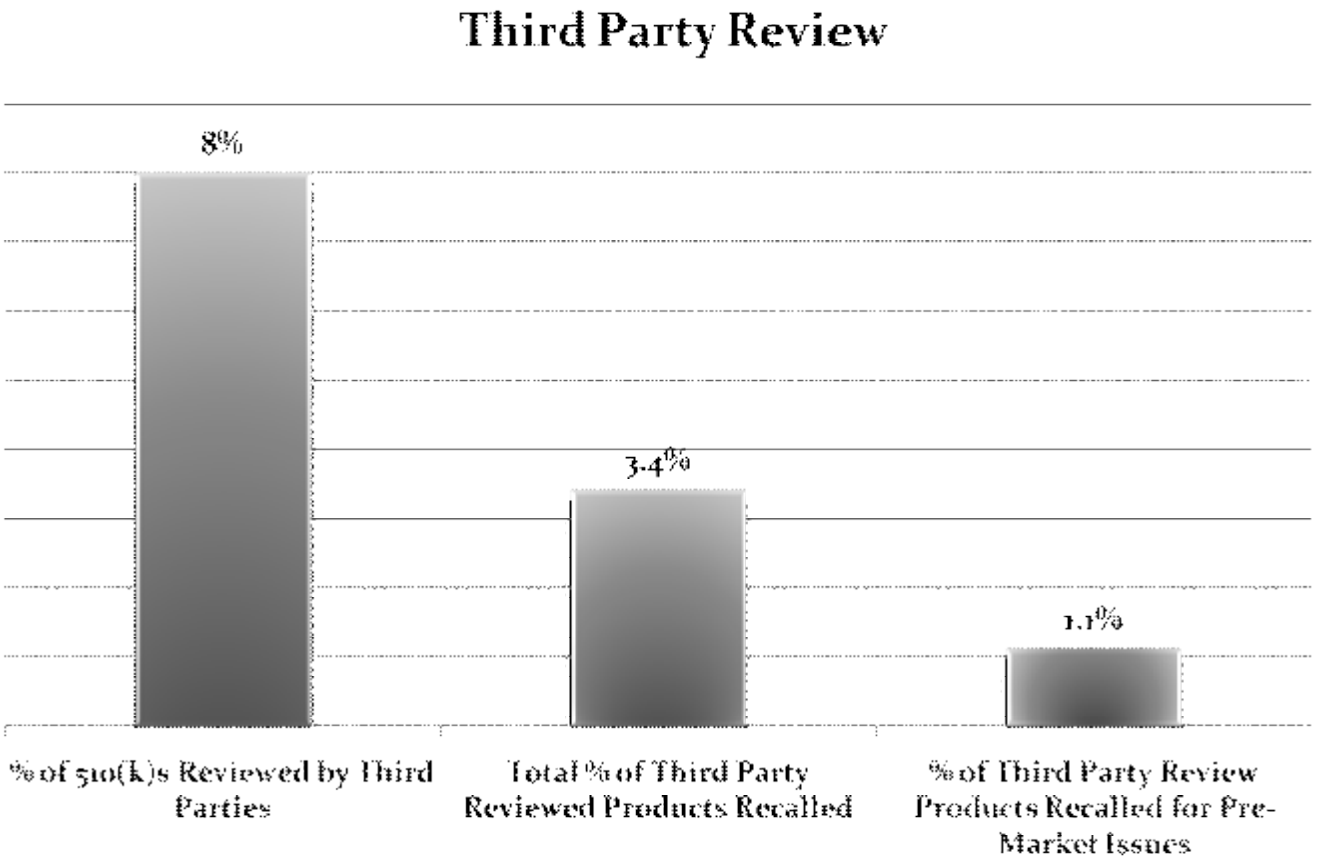
Excluding AEDs and infusion pumps doesn't change the ratio of premarket issues

22% of products are implantable

Data is essentially what would be expected



3rd Party Review System not Linked to Recalls



Conclusions and Open Questions

Introductory Thoughts

- Opinions are mine alone
- Research did not address other key issues
  - Patient access/autonomy
  - Innovation
  - Cost
  - Administrative issues
- Strong desire to make changes based on data
  - “Ready, fire, aim” never works
  - Changes can have a negative effect
  - Avoid policy by anecdote
- No one can deny that there have been at least some meaningful safety recalls

Key Conclusions

- Based on Class I (safety) recalls, FDA has an excellent record
  - ~99.8% of product submissions did not experience a Class I recall in a 5 year period
- Is ~99.8 % “correct” decisions a mark of success or failure?
  - It can never be -0-
  - Personally, I’m fairly impressed
- Importance of QSR
  - Probably much more important than additional human testing

Other Conclusions

- Majority (55%) of recalls are due to post-market issues
- Issues exist with certain product types (AEDs and infusion pumps)
  - Product specific “rules” may be the answer
  - Up classification?
  - Ongoing review need of recall patterns
- Benefit of ongoing review of recalls
  - Early identification and intervention for problem product types

Other Conclusions

- Additional human testing pre clearance would seem to be of limited value
  - Few undiscovered clinical issues
  - Different than pharma issues
  - Role of human factors
- Design controls, bench testing and preclinical studies would appear to be more effective and more ethical
- Hard to determine whether pre-clearance inspections would add meaningful data
  - Additional issue regarding resources and time
- Implantable devices seem to operate as predicted

Other Conclusions

- PMA and 510(k) systems seem to yield similar results
- Many product types have few or no recalls
  - Concentration in AEDs and infusion pumps
- Hard to define a logical "4th class" of devices based on safety needs
  - Orthopedics is often the example but very few recalls of orthopedic products
- Data supports importance of QSR systems
  - Design controls
  - Manufacturing controls
- Third party review system seems to work

Open Questions

- What role, if any, did post market surveillance have in identifying recall needs
  - What aspects of post market surveillance have the greatest impact?
- What are the true root causes of these safety recalls?
  - What lessons for submissions What are the common factors that drive AEDs and infusion pumps recalls
  - Human factors?
  - Complexity?
- Potential impact of 510(k) changes
  - FDA resources and time
  - Will added burden of changes have a proportional benefit on safety
  - Impact on access

Open Questions

- Date relationship between events
- What parts of submissions make a difference?
  - E.g. does the manufacturing section of a PMA improve safety decisions?
- What role did multiple or split predicates have in recall situations?
- Hard to link a premarket issue to the first 510(k) or specific PMA/sPMA
  - Additional detail here would be interesting
  - Are we (FDA, industry, HCPs) learning from past events?

Questions or Comments?